

Accelerating PKPD Analysis with Automated DDI Variable Creation: A SAS-Based Approach.

Paper SM08

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Bio

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Consultant with 15 years of SAS/R programming experience in analytical solutions turning data into actionable business insights. Demonstrable experience with statistical data analysis, regression, sensitivity analysis and predictive modeling. Expertise in working with large datasets to solve complex business problems in the pharma sector. Skilled in utilizing advanced AI tools, with consistent effort in exploring their functionalities, applications, limitations and practical use cases.

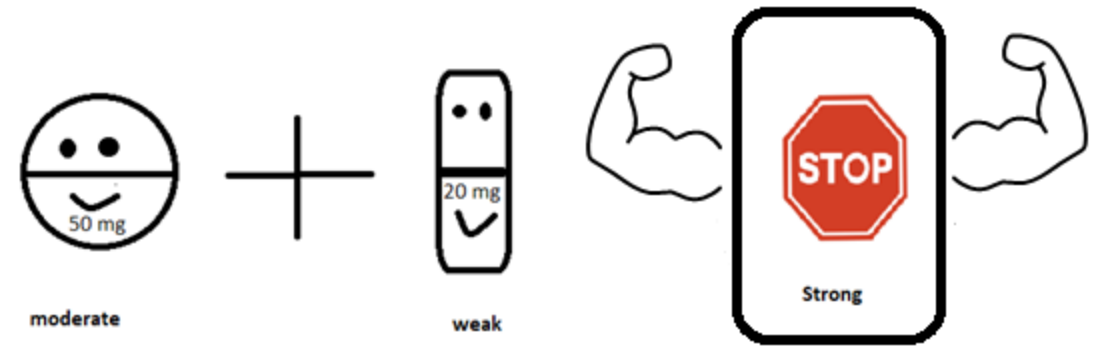


Bio (cont.)

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Associate Director

Sunil Mummidisetty is Associate Director at Certara where he leads US data programming team that creates analysis ready PK/PD datasets for clients. He has worked across all phases of drug development with deep expertise in PKPD analysis dataset development. He has over 19 years of experience in programming and reporting in Pharmaceutical & CRO environment. Prior to joining Certara, Sunil worked as a Lead PKPD & SAS Programmer for Pfizer and CSL Behring.



Drug-Drug Interaction

Drug-drug interaction (DDI) occurs when two or more drugs react with each other when taken simultaneously, which can change how the drugs work potentially impacting the overall therapeutic effect and safety of the treatment (as these can cause unexpected side effects).

Also, In Vitro (lab) effects need not translate into In Vivo effects. There maybe some drug effects which are observed in the labs but in the real world need not translate to effects on a living organism. So, the list of drugs and their effects on the various enzymes must be clearly understood along with the basis of classification (In-Vitro or In-Vivo).



Motivation

The reason behind the interest to explore and look at concomitant medications drug effects in the pharmacometrics analysis would be to understand more regarding the following -

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- Do moderate/strong CYP3A4 or other CYP inhibitors lead to higher investigational drug exposures?
 - Do moderate/strong CYP3A4 or other CYP inducers lead to lower investigational drug exposures?
 - Do acid-reducing agents (ARAs) or proton pump inhibitors (PPIs) lead to higher or lower investigational drug exposure?
 - How do drug transporters like Human breast cancer resistance protein (BCRP) affect some of the tumor related analysis?

When we say the automation looks at drug-drug interaction, essentially, we are thinking on the above lines based on the characteristics of the investigational drug, whether it has some basis to believe for us to explore along those lines as drug-drug interactions affect the drug metabolism (including key PPK parameters like clearance etc.) in turn affecting the drug exposure.



What are CYP's and why the interest in these?

Exploration of DDI is from the perspective of how these medications inhibit or induce the **cytochrome P450 (CYP) enzymes** in the liver, which are **responsible for metabolizing many drugs in the body**, meaning they can significantly affect how other drugs are processed and potentially lead to harmful drug interactions when taken together; Essentially, they have a significant impact on the metabolism of other drugs due to their potential CYP activity.

“Of all the different CYP proteins that are present in the human body, six of them are involved in the metabolism of 90% of drugs. These proteins are CYP1A2, CYP2C9, CYP2D6, CYP3A4, and CYP3A5. The most important are CYP3A4 and CYP2D6” **
(<https://www.ncbi.nlm.nih.gov/books/NBK557698/>)

So, in the creation of time-varying DDI variables, we are **essentially interested in** creating time-varying categorical variables of **(CYP3A or CYP2D6, two most prominent CYP enzymes that affect majority of drug metabolism) and PPI/ARA**. Depending on the investigational drug characteristics, we could also look at other CYP's of interest.

To read more on these, including the output variables from the automation, please refer to the appendix section of the paper.



Introduction and Context

Creating time-varying drug-drug interaction (DDI) variables is essential but often time-consuming in PKPD dataset construction. Considerable effort is spent to address the following challenges:

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- 1) Inconsistencies in Drug Names captured in the dataset
 - 2) Incomplete Documentation or Missing data
 - 3) Lack of usage of appropriate Interaction Time Window
 - 4) Identifying relevant drugs of interest from multiple sources
 - 5) Multiple versions in WHODrug formats in CM dataset
 - 6) Need for repeated review of changes in guidelines

Our SAS-based standardized script automates this process, leveraging a continuously updated internal database of drug lists and potencies, curated by our DIDB clinical experts. This has led to substantial efficiency and quality gains.

Challenges in DDI

- **Inconsistencies in Drug Names captured in the dataset**

Alternate names/ Synonyms: Prednisolone sodium hemisuccinate is also known as Meticortelone Soluble.

Different Formulations: Salt forms may also be appended to the main drug

Select the value/s for column CMDECOD

Lookup Values

PREDNISOLONE
PREDNISOLONE HEMISUCCINATE
PREDNISOLONE SODIUM SUCCINATE
PREDNISONE
PREDNISONE ACETATE

Select the value/s for column CMDECOD

Lookup Values

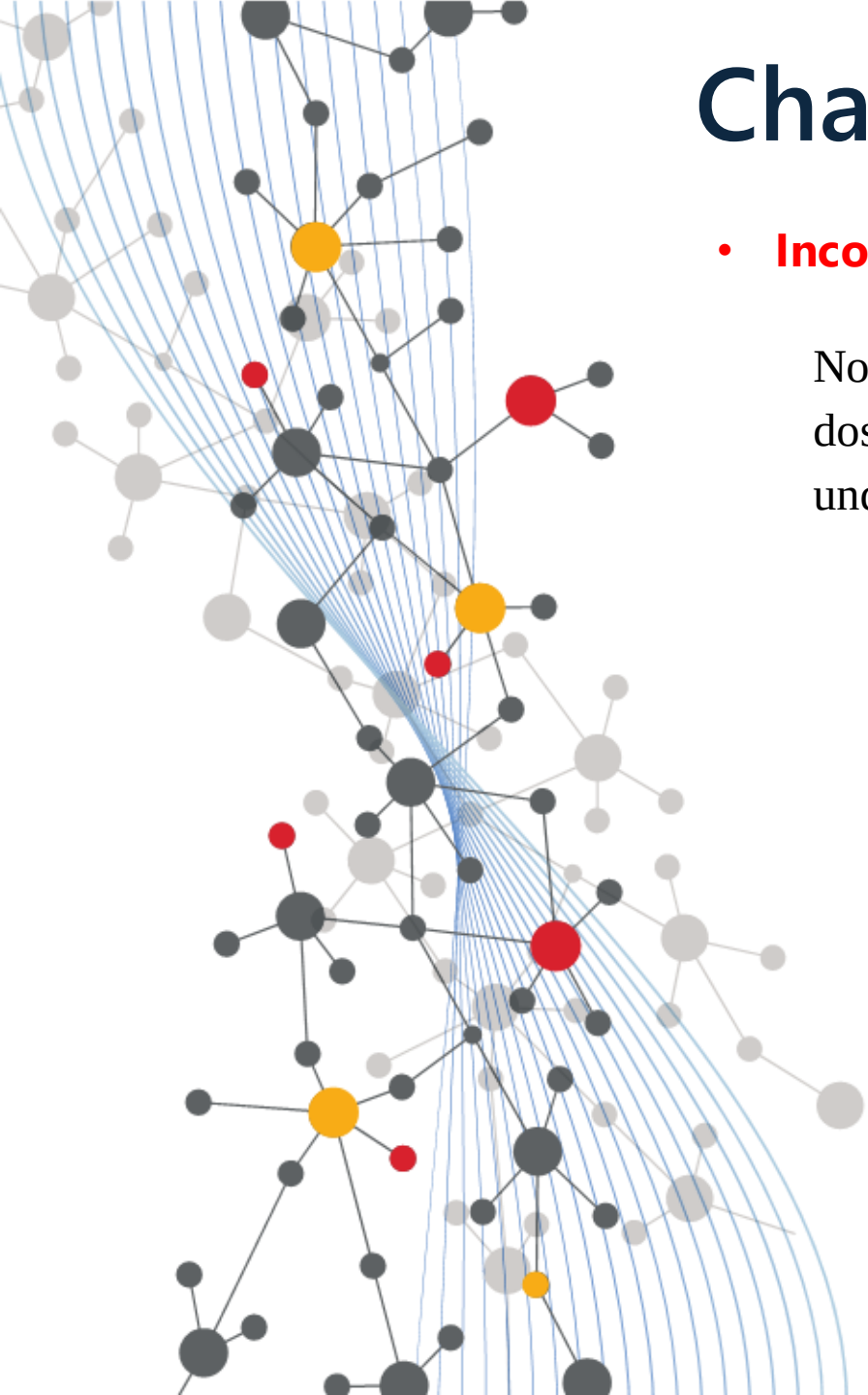
CETIRIZINE
CETIRIZINE HYDROCHLORIDE
CHLORPHENIRAMINE SUCCINATE

Select the value/s for column CMDECOD

Lookup Values

ISAVUCONAZOLE
ISAVUCONAZONIUM
ISAVUCONAZONIUM SULFATE

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Challenges in DDI

- **Incomplete Documentation or Missing data**

Not all concomitant medications or their complete details (e.g., start and stop dates, dose amounts, frequencies) are consistently reported. Missing data can result in underestimating the prevalence and impact of DDIs.

Some of the missing information can be addressed using best judgement or assumptions listed below:

The problem of missed conmed date times (start and stop) can be overcome by the below logic –

- If the Start Date is partial like YYYY or YYYY-MM, we can use the first month and first day of the month etc. and append it to the partial information to get a good estimate of Start Date.
- Similarly, if the End Date is partial like YYYY or YYYY-MM, we can use the last month and last date of the year or last date of the month etc., to get an exhaustive period when co-medication may have been taken.
- We can also make provisions for filling the missing months or dates as per Leap Year or not considerations. E.g., if the CMSTDTC was 2024-02, we can fill it as 2024-02-29 as 2024 is a leap year.

Challenges in DDI

- **Incomplete Documentation or Missing data (example)**

CMSTDTC	CMSTDTC after filling with closest match
2024-02	2024-02-01
2021	2021-01-01

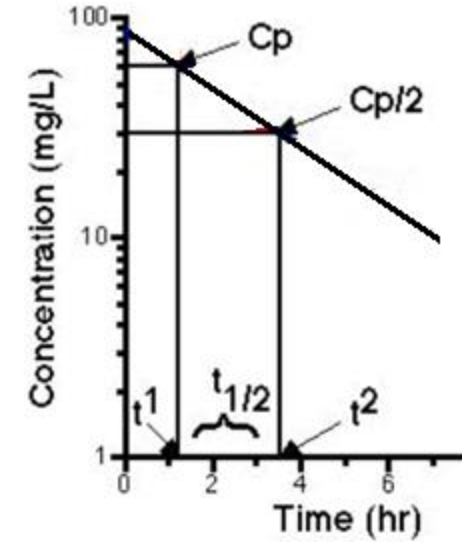
- If CMENDTC is missing completely or blank and another CM column, like CMENRF or CMENRTPT or CMONGO etc. has the value ONGOING or AFTER, we can fill the CMENDTC as the date on which the script is being run or the last date of the year when the script is being run to be consistent and exhaustive in the conmed date range.

CMENDTC	CMENRF/ CMENRTPT/ CMONGO	CMENDTC after filling with closest match
2020-02		2020-02-29
2020		2020-12-31
	ONGOING	2025-12-31
	ONGOING	2025-01-30

Challenges in DDI

- **Lack of usage of appropriate Interaction Time Window**

Effects of a drug on the enzyme can linger in the body long after it has been stopped depending on the half-life of the drug. E.g., “The induction of CYP3A4 by rifampicin takes around six days to develop and 11 days to disappear” – **Reference: Hukkanen J. 2012. Induction of cytochrome P450 enzymes: a view on human in vivo findings. *Expert Review of Clinical Pharmacology* 5: 569–585**



- The induction period of a drug is the time it takes for a drug to increase the production of a cytochrome P450 (CYP450) enzyme.
- The half-life of a drug is the time it takes for a drug's active substance in the body to reduce by half.
- Depending on the pharmacokinetics or half-life of the drugs involved, we might need to consider a specific time window for interaction analysis (slightly bigger window than the actual conmed dates)
- Drugs with a shorter half-life induce enzymes more quickly and conversely longer half-life drugs induce enzymes slowly. E.g., rifampicin has a half-life of 2–3 hours and can induce enzymes within 24 hours, while phenobarbital has a half-life of 3–5 days and can take about a week.

Disclaimer: Image at the top-right of the slide obtained from the web (public domain) for illustration purposes only.



Challenges in DDI

- **Identifying relevant drugs of interest from multiple sources**

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- There are various repositories that list drugs, their potencies and effect on enzymes (FDA, DIDB, Flockhart Table etc.).
 - Finding a well documented list of all the drugs with latest information in one place is hard.
 - It is necessary for every team to compile a master list of these from various sources to get a better assessment of the drugs and their impact on the enzymes.
 - Periodically this list must be reviewed by subject matter experts and updated if more drug interactions are found with regards to the respective CYP enzymes of interest.



Challenges in DDI

- **Multiple versions in WHODrug formats in CM dataset**

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- When pooling studies of a sponsor together and analyzing the data, we should be aware that the earlier studies could have used prior formats of WHODrug standards and may not adhere to latest formats. This increases the complexity in the approach used to pull the drugs from the dataset.
 - For e.g., “In the B2/C format, the generic names were displayed by appending ‘w/’ followed by the substance name, whereas in the B3/C3 format, the generic name is separated by a semicolon (;) when multi-ingredient generic names of drugs are captured in the CM dataset” - **Reference: PharmaSUG 2020 - Paper DS-109 Impact of WHODrug B3/C3 Format on Coding of Concomitant Medications**



Challenges in DDI

- **Need for repeated review of changes in guidelines**

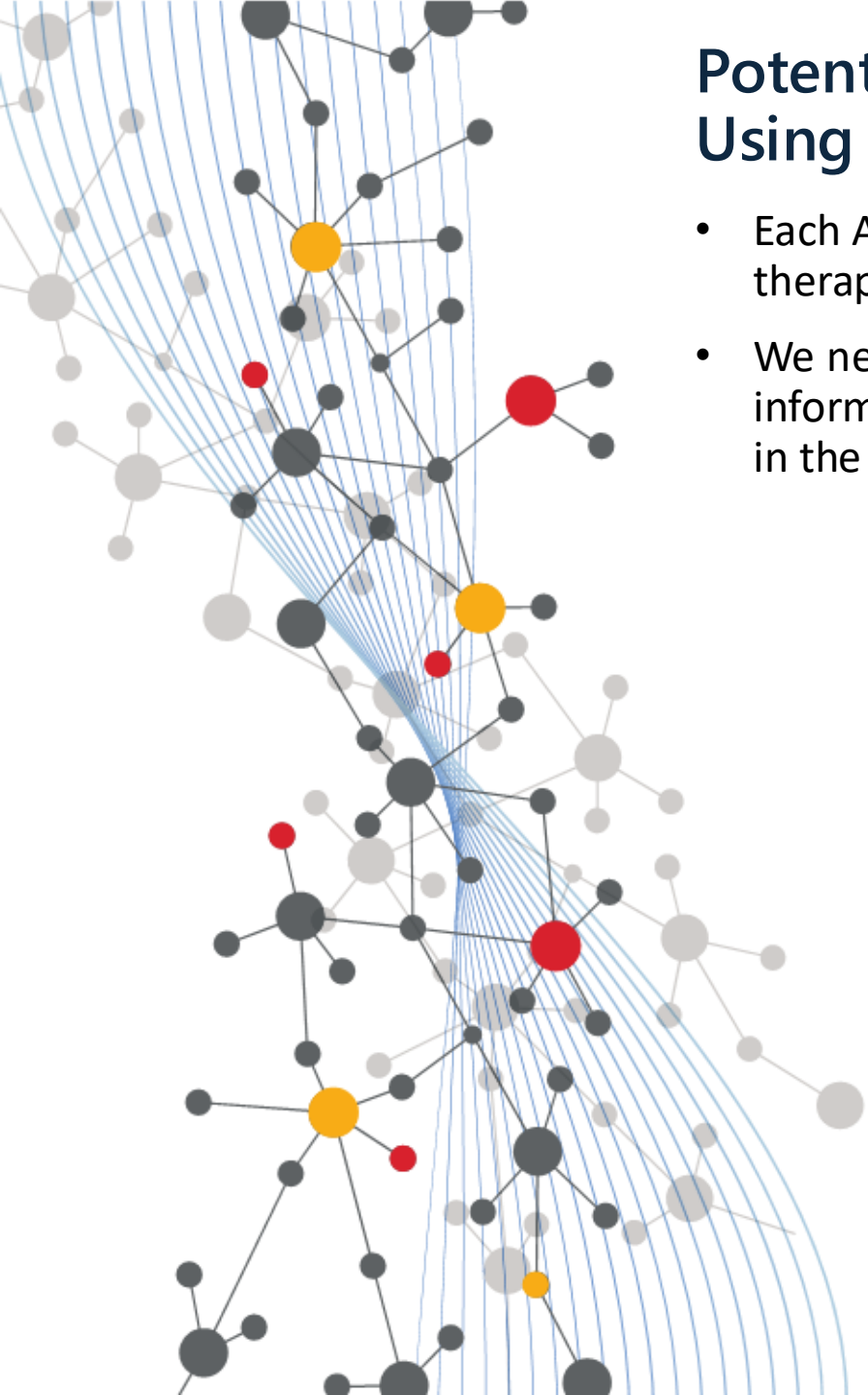
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- According to the CDISC SDTMIG v3.3, the first 200 characters of text should be stored in the variable and each additional 200 characters of text should be stored as a record in the SUPP—dataset.
 - For drugs with many ingredients, the generic name is longer than 200 characters. The SAS export format has a limitation to 200 characters per field, if this format is used for submission, the supplemental dataset needs to be utilized. **Reference:** <https://who-umc.org/media/2940/how-to-use-whodrug-for-compliance-with-cm-domain-in-the-cdisc-sdtm-standard-march-2017.pdf>
 - It is important to understand that SUPPCM may also contain important drug information and hence, we need to look at both CM and SUPPCM domains.



Potential Solution for Inconsistencies in Drug Names – Using Partial String Searches

- To search for drugs in the CM/SUPPCM dataset, we need to use partial strings and pattern matching and searching within strings. We can use either of two choice of functions for this –
 - ☐ Use **INDEX** when you need to perform simple substring searches and prioritize performance.
 - ☐ Use **PRXMATCH** when you need to perform complex pattern matching with regular expressions.
 - Although using partial strings can help provide information on potential drug effects, in extreme cases, it can also act counterintuitively (such as resulting in False Positives).
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- For e.g., Aprepitant and Fosaprepitant are moderate and weak CYP3A4 inhibitors, respectively. Fosaprepitant is considered a prodrug of Aprepitant, meaning that when administered, the body rapidly converts Fosaprepitant into the active drug, Aprepitant;
 - In searching for Aprepitant we can end up flagging both records that contain Aprepitant and Fosaprepitant as well. This can potentially misclassify the drug potencies if not reviewed and validated by a Subject Matter Expert (SME).
 - Once validated by the SME, these drugs can be built in as special cases inside the automation mapping the correct potencies.

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Potential Solution for Inconsistencies in Drug Names – Using ATC codes

- Each ATC code represents a specific group of medications based on their therapeutic use and chemical characteristics.
 - We need to look at relevant information in the CM and/or SUPPCM for this information. Although, the earlier or legacy studies may not have this captured in the latest standards, this is also a potential solution we could explore.
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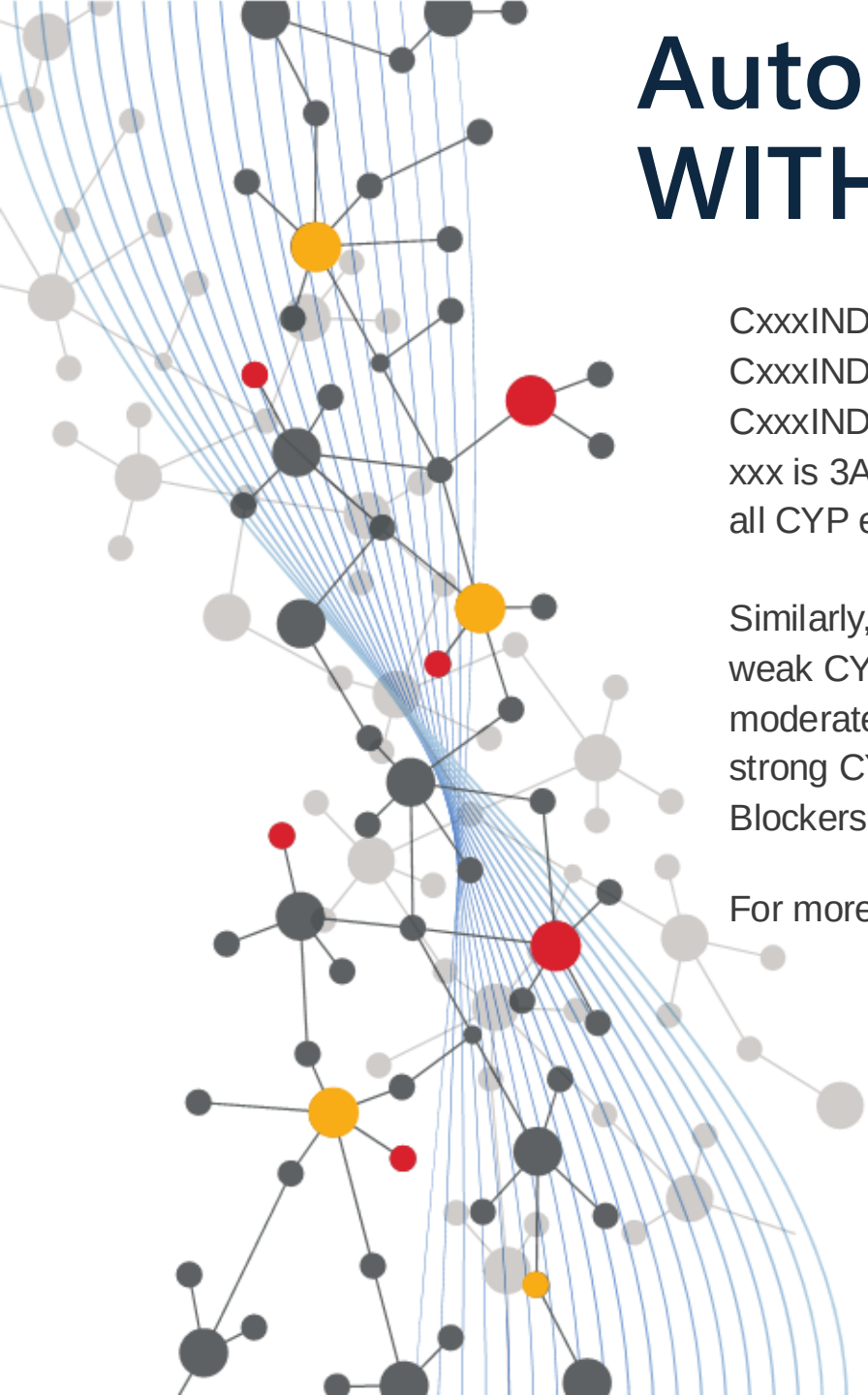
Automation enables Validation by Subject Matter Experts

- We can confirm from SME or the sponsor if we have any question about drug potency effects if there are combination of drugs involved or if the search string is not the same as the one in the dataset.
- Following is a snippet of sample supplemental output from the script.

VERIFY_THESE with values of 1 - Please confirm with the sponsor and/or modeler if okay to map them under the given potency and DDI variables

Potency Classification	Search String	Standardized Medication Name	Unique Subject Identifier	Start Date/Time of Medication	End Date/Time of Medication	Study Day of Start of Medication	Study Day of End of Medication	End Relative to Reference Period	VERIFY_THESE
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN	M A S K E D I N F O	2023-03-13		210	.	AFTER	0
Strong Inhibitor	IDELALISIB	IDELALISIB		2018-01-05	2021	-1900	-444		0
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN		2023-12-04	2023-12-08	189	193		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2014-10-22	2015-05-08	-2842	-2644		0
Strong Inhibitor	VORICONAZOLE	VORICONAZOLE		2023-04-04	2023-04-06	35	37		0
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN		2023-09-19	2023-09-24	386	391		0
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR		2022-07-19	2022-07-23	183	187		1
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR		2022-07-19	2022-07-23	183	187		1
Strong Inhibitor	IDELALISIB	IDELALISIB		2022-09-30	2022-10-17	103	120		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2021-11-23	2021-12-10	-21	-4		0
Strong Inhibitor	IDELALISIB	IDELALISIB	I N F O	2023-09-08		459	.		0
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR		2023-11-02	2023-11-06	79	83		1
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR		2023-11-02	2023-11-06	79	83		1
Strong Inhibitor	IDELALISIB	IDELALISIB		2018-11-23	2020-04-13	-1713	-1206		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2023-08-01	2023-11-27	-125	-7		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2022-10	2023-05	.	22		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2022-12-08	2023-01-19	-102	-60		0
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN LACTOBIONATE		2023-09-28	2023-10-03	67	72		1
Strong Inhibitor	IDELALISIB	IDELALISIB		2014-09-30	2016-05	-3352	-2743		0
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN LACTOBIONATE		2023-12-18	2023-12-24	113	119		1
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR		2023-03-24	2023-03-24	484	487		1

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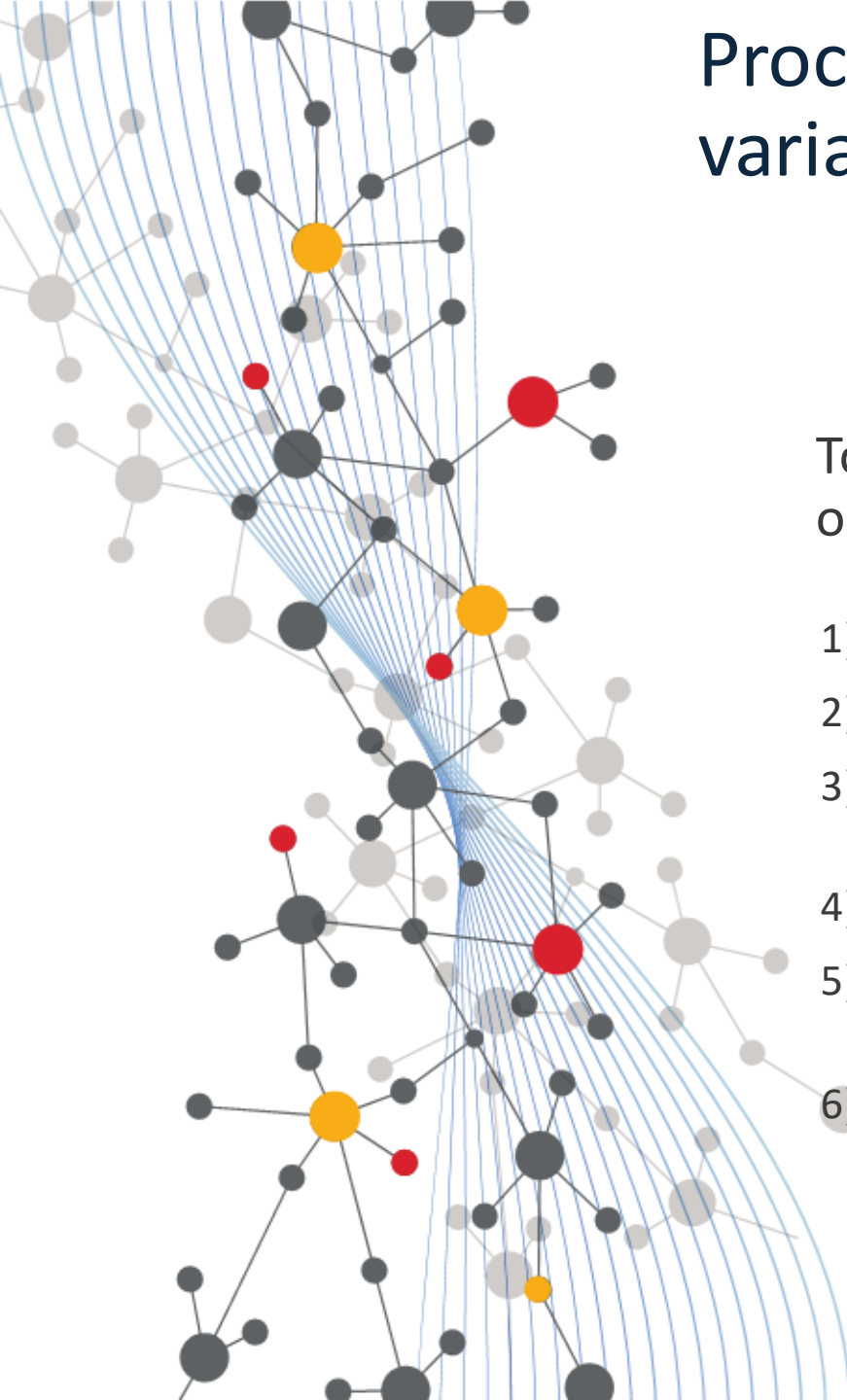
Automation – Sample Output WITH TIME-VARYING DDI VARIABLES

CxxxINDW (0=absence of weak CYP3A inducers; 1=presence of weak CYP3A inducers;)
CxxxINDM (0=absence of moderate CYP3A inducers; 1=presence of moderate CYP3A inducers;)
CxxxINDS (0=absence of strong CYP3A inducers; 1=presence of strong CYP3A inducers;) where
xxx is 3A4 or 2D6 (most popular two CYP's that affect more than 80% of all metabolisms among
all CYP enzymes).

Similarly, inhibitor variables are CxxxINHW (0=absence of weak CYP3A inhibitors; 1=presence of
weak CYP3A inhibitors;) CxxxINHM (0=absence of moderate CYP3A inhibitors; 1=presence of
moderate CYP3A inhibitors;) CxxxINHS (0=absence of strong CYP3A inhibitors; 1=presence of
strong CYP3A inhibitors;) PPI (0=absence of PPI; 1=presence of PPI;) H2A (0=absence of H2-
Blockers; 1=presence of H2-Blockers;)

For more related information, please refer to the appendix of the paper.

ID	TIME	C3A4INDW	C3A4INDM	C3A4INDS	C3A4INHW	C3A4INHM	C3A4INHS	PPI	H2A
1	0	1	1	0	0	0	0	0	0
1	1	1	1	0	0	0	0	0	0
1	3	1	1	0	0	0	0	0	0
1	8	1	1	0	0	0	0	0	0
1	20	1	1	0	0	0	0	0	0
1	32	1	1	0	0	0	0	1	0
1	44	1	1	0	0	0	0	1	0
1	56	1	1	0	0	0	0	1	0
1	68	1	1	0	0	0	0	1	0
1	80	1	1	0	0	0	0	1	0



Process Flow to automate Time-Varying DDI variable creation

To automate and expedite the Time-Varying DDI variable creation one must consider the following items –

- 1) Compile a master database and update frequently
- 2) Review the master database of drugs and their potencies by SME's
- 3) Give provisions for accommodating interaction period i.e., Provide a Delta window option through code that will increase the interaction period (induction mostly).
- 4) Think about choice of functions to filter the drugs from CM
- 5) Export supplemental information as a html file that contains drug list from CM to verify with the sponsor or SME when combination of drugs are involved.
- 6) Refine list based on suggestions and export the DDI variables as different categorical or binary variables to analyze the cumulative effects of different drugs

Additional Considerations using illustrative scenarios

Question 1: "Anaemia" is the British spelling, while "anemia" is the American spelling. We usually find a lot of data capturing or inconsistencies in CM or AE. What can we do to overcome or mitigate some of the discrepancies in drug names due to different formulations, various spellings, or genuine mistakes while logging data?

Answer: Usage of SOUNDEX, COMPGED, DIFFERENCE functions etc.

```
data names;
  input name $30.;
  soundex_code = soundex(name);
  datalines;
anemia
anaemia
anemya
Anemic
Anemiaically
Cetrizine hydrochloride
Cetzine
Cetsine
cetirizine
isavuconazonium
isavuconazonium sulphate
isavuconazonium sulfate
isavuconazole
;
run;

proc print data=names;
run;
```

Obs	name	soundex_code
1	anemia	A55
2	anaemia	A55
3	anemya	A55
4	Anemic	A552
5	Anemiaically	A5524
6	Cetrizine hydrochloride	C3625362463
7	Cetzine	C325
8	Cetsine	C325
9	cetirizine	C3625
10	isavuconazonium	I2125255
11	isavuconazonium sulphate	I21252552413
12	isavuconazonium sulfate	I21252552413
13	isavuconazole	I212524



Additional Considerations using illustrative scenarios (cont.)

Question 2: If we don't have the DELTA (correction factor or window of DDI consideration) information, what do we set DELTA values as ?

Context: Depending on the pharmacokinetics or half-life of the drugs involved, we might need to consider a specific time window for interaction analysis. So, we will have to provide a delta/window variable that can accommodate a slightly bigger window than the actual conmed dates. The correction window or extension of the conmed dates information will be provided to the programmers by the modeler.

Answer: Ideally modelers would provide what values to consider for DELTA. But, if no information is provided, by default DELTA value can be considered as 0 or no changes to the existing information of start and stop date times of conmeds. We will assume and treat conmeds got cleared from the body and there is no DDI after the end of conmed end date and time in this situation.



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